PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, 47/48, 47/36, 47/38

A1

(11) International Publication Number: **WO 98/11874**

(43) International Publication Date: 26 March 1998 (26.03.98)

(21) International Application Number: PCT/SE97/01592

(22) International Filing Date: 22 September 1997 (22.09.97)

(30) Priority Data:
9603480-6 23 September 1996 (23.09.96) SE

(71)(72) Applicant and Inventor: CARLFORS, Johan [SE/SE]; Prästgårdsgatan 13C, S-752 30 Uppsala (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: LINDELL, Katarina [SE/SE]; St. Hans Gränd 38B, S-226 42 Lund (SE).

(74) Agents: BERG, S., A. et al.; H. Albihns Patentbyrå AB, P.O. Box 3137, S-103 62 Stockholm (SE).

(81) Designated States: AU, CA, CN, JP, KR, RU, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
In English translation (filed in Swedish).

(54) Title: PHARMACEUTICAL COMPOSITION FORMING A GEL

(57) Abstract

An in situ gel forming pharmaceutical composition for local administration to a target organ in the body, said composition essentially consisting of a water solution containing one or more aggregate forming surfactants, one or more gel forming water soluble polymers, a drug and optionally excipients, said drug having lipophilic properties, as it binds stronger to the aggregates of surfactants than to water, whereby its release from the in situ forming gel to the target organ occurs slowly.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

Pharmaceutical composition forming a gel

The present invention relates to a pharmaceutical composition forming a gel and in particular to a pharmaceutical composition, which after administration is transformed to the form of an in situ gel.

Drugs can be administrated to the body in various administration forms, e. g. solutions, suspensions, emulsions and gels. In the following gels will be described. A gel can be fluid before administration to a patient, to form after administration to the proper body organ, a gel, a so called "in situ" gel. The formation of the gel is accomplished by factors in the surroundings at the place of administration. Examples of such factors are the presence of electrolytes and proteins. Other factors that can cause formation of a gel are temperature and pH.

To produce in situ gels is known by for instance B. Cabane, K. Lindell, S. Engström and B. Lindman, "Microphase Separation in Polymer + Surfactant Systems" Macromolecules 1996, 29, p 3188-3197. It is disclosed therein how ionic surfactants dissociate a polymer rich phase into smaller parts. Examples of polymers disclosed are ethylhydroxyethyl cellulose (EHEC) forming a clear solution with timololmaleate (TM). Phase studies showed that thermoreversible gels are formed, i. e. that a clear solution at ambient temperature transforms to a transparent gel at higher temperature, such as 35 °C and vice versa.

Another method of producing an in situ gel is to use for instance Gelrite®, which forms a gel when adding an electrolyte, which is disclosed in Carlfors J., Edsman K., Peterson R., and Jörnving K., "Rheological evaluation and ocular contact time of Gelrite® in situ gels for ophthalmic use", submitted to Eur. J. Phar.. Sci. (1996).

In for instance E. D. Goddard, " Polymer/surfactant interaction", J. Soc. Cosmet. Chem., 41, 23-49 January/February 1990 the use of water soluble polymers and surfactants is disclosed. It is shown that the surfactants form aggregates or clusters and are associated to the polymer.

In Edsman K., Carlfors J., Harju K., "Rheological evaluation and ocular contact time of some carbomer gels for ophthalmic use", International Journal of Pharmaceutics 137, p 233-241, 1996, is disclosed the problem with poor uptake of many drugs in the eye due to the fact that tear liquid eliminates the drug in the eye before it has had time to work. Thus, an extended take up time is

desirable, which is accomplished by the use of gels instead of common solutions. Especially the rheology of the gels is disclosed.

Carlfors J., Edsman K., Peterson R., and Jörnving K., " Rheological evaluation and occular contact time of Gelrite® in situ gels for ophthalmic use", submitted to Eur. J. Pharm. Sci. (1996) gives examples of administration forms in the form of in situ gels, which remain longer in the eye after administration than water solutions and dispersions. The reason is their rheological properties. A high elasticity modulus and a lower viscosity modulus, resulting in an elastical consistency having low fluidity, well resisting elimination by tear flow and blinks.

Thus, a long residence time for the drug is very desirable. One way of accomplishing this is as above mentioned to add a gel forming polymer to a suspension. Especially favourable "in situ gels" have shown to be, because they can easily be dosaged by conventional dropping into the eye. When the drop lands in the eye liquid it is changed partly due to exchange with the surroundings, leading to a physical-chemical change of the administration form, promoting the gel formation.

SE-B-9003712-8 and EP-B1-0 227 494 both disclose "in situ" gels. However, both documents disclose water soluble hydrophilic drugs, and the later also suspensions. However, water soluble drugs have the disadvantage that they , after administration of the in situ gel forming drug, are not retained in the gel, but are relatively fast diffusing out from the gel and eliminated from the eye. If instead drugs are used in the form of suspensions in the gels of interest, the release rate is determined by the dissolution rate of the drugs, thereby limiting the applicability of the administration form of drugs having suitable dissolution rate, besides the problem with reproducible dosage and physical instability, which exists in suspensions.

The advantages of using "in situ" gels as administration form for drugs are well-known. The fluid consistency enables a simple dosage, and at the same time the transformation to gel with its elastic characteristics and lower fluidity often result in a longer contact time for the administration form at the administration site, for instance in the eye compared to a corresponding liquid aqueous solution or suspension. Thus, the gel better resists natural elimination mechanisms, such as e. g. body fluid flow and mechanical influence.

The advantage is most evident in connection with local administration of the drug, for instance in the eye, because the drug in the administration form is designed for local absorption. If the

retention time of the drug is increased, the ability for a larger proportion of drug to be absorbed before the administration form has been eliminated from the eye is increased.

Thus, a common problem with prior art administration forms, which form gels in situ, is the often insufficient active time (depot effect) at the site of administration, for instance the eye.

The object of the invention is to solve the above problems. This is accomplished by a pharmaceutical composition according to claim 1.

The slow release of these drugs having lipophilic properties from the in situ gel forming pharmaceutical composition in combination with the long contact time of the composition at the site of administration, will give rise to an extended local duration, as regards the therapeutical effects of the drug. It can also lead to a larger proportion of dosaged drugs being absorbed to target organs, e. g. mucous membranes compared to conventional administration forms.

Thus, a great advantage with the in situ gel forming pharmaceutical composition according to the invention is that a long contact time is accomplished; sometimes only a single drop of the composition is needed for so long time as 24 h, compared to prior art, where repeated dropping was required several times per 24 h.

The invention accomplishes a favourable slow release of drugs from the formed gels. Through the slow release a therapeutically acceptable concentration can be emitted for a long time by a single dropping. This brings about large advantages for a patient. The long contact time in the eye is also expected to cause an increased absorption of the drug to the eye, leading to higher effect, or alternatively the dosage can be lowered with maintained effect. Furthermore, lower dosages of the drug can often advantageously be used, diminishing discomfort and/or side effects.

The invention is applicable within the ophtalmological field. The drug can be administered by dropping into the eye. Due to tear drainage, blinkings and specific absorption, the drug is eliminated in for instance approximately 5-20 minutes after dropping into the eye. During this contact time, the drug shall be absorbed to superficial target organs, for instance when treating conjunctivitis, or transported through the cornea to reach target organs in the eye, for instance when treating glaucome. An increase in the residence time for the drug in the eye is favourable in both cases. In the first case, it can lead to a higher proportion of absorbed drug, and that the

duration of the therapeutical effect is extended. In the second case, the extended contact time in the eye results in that the time for transport of drug through the cornea increases, which may result in higher absorption and also an extended duration of the therapeutical effect of the drug.

In accordance with the invention a favourable slow release of drugs from the formed gels is achieved. By the slow release a therapeutically acceptable concentration is emitted for a long time with a single dropping. This results in great advantages for a patient. The long residence time in the eye is also expected to give an increased absorption of drug to the eye, leading to a higher effect, or alternatively the dosage can be lowered with maintained effect.

Herein "in situ" gel forming refers to a solution, which after administration to a target organ, e. g. an eye, forms a gel thereon. Such a gel formation can be accomplished by the interaction of a polymer and a surfactant, in that the surfactant dissociates the polymer into smaller pieces, whereafter the surfactant places itself on the polymer pieces, giving rise to a more gelatinous consistency. Detailed description of the gel formation is disclosed in B. Cabane, K. Lindell, S. Engström and B. Lindman, " Microphase Separation in Polymer+Surfactant Systems", Macromolecules 1996, 29, p 3188-3197, incorporated herein by reference. The system discloses a thermoreversible gel. Another example is as mentioned above Gelrite®, forming a gel in the presence of electrolytes. As is evident from the document, surfactants are not necessary to obtain an in situ gel.

Herein "aggregate" refers to co-operatively linked micelle like aggregates consisting of a large number of molecules of surfactants, being associated, i. e. are linked to the polymer. A closer definition is given by E. D. Goddard, "Polymer/Surfactant interaction", J. Soc. Cosmet. Chem., 41, 23-49 January/February 1990, which is incorporated herein by reference.

"lipophilic properties" means that the affinity to lipophilic environment is large, for example to the aggregates of surfactants, i. e. the preference for water is small ("poor" "solubility in water"). The drug can be imparted such properties by conventional treatment, for example latanoprost, which is a prodrug.

The drugs having lipophilic properties are dissolved into polymer-associated aggregates of surfactants. The release from formed gels becomes slow due to the lower affinity to water compared to that of the aggregates of surfactants. Therefore, the gels can act as depots, i. e. storage places for drugs, as long as they remain at the administration site. The duration for the

release from these depots increases the stronger the drug is associated to the aggregates. Normally it has shown that the rate of release decreases with increasing distribution coefficient K_D (octanol/water), which defines the magnitude of the affinity to a certain phase for the drug. Other factors that can influence the rate of release is the affinity for the drug to the aggregates of surfactants, the electrostatic charges of the drugs and/or the polymer (if the polymer is charged) and the aggregates, and the osmolality of the composition. High affinity involve a strong association of the drugs to the aggregates and a slower release. For a charged polymer, a so called polyelectrolyte, the surfactant should have an opposite charge for a strong association between the polymer and the surfactant to be reached. The osmolality of the composition affects the release in that it will be faster if the osmolality of the composition exceeds the osmolality of the receiving media. If the osmolality of the composition falls below that of the receiving media, the mass transports will be the opposite.

A pre-requisite to reach these favourable effects is; however, the presence of polymer associated aggregates of surfactants in the composition. The lipophilic drugs associate to the aggregates and due to the low solubility of the drugs in water, the release from the aggregates to the tear liquid will be slow.

The rate of release can be controlled and determined by the degree of affinity, electrostatic charges, the osmotic balance between the administration form and the body fluid, and ratios of amounts between drug and surfactant.

If the capacity of solubility of the composition is exceeded, a mixture of dissolved drug and particles of drug substance is obtained. In such a case the release is controlled both by the diffusion from dissolved drugs from the polymer associated aggregates of surfactants and also of the dissolution rate of the drug particles.

As polymers in the composition polysaccharides are preferred, in particular ethylhydroxy cellulose, deactetylated gellan, karrageenan, alginates and hyaluronic acid.

A specific example of a polymer is Gelrite®, commercially available from Kelco Division, Merck Sharp and Dome, consisting of deactylated gellan gum, which forms a gel due to cations in the eye.

As surfactants the composition can comprise, ionic, amphoteric as well as non-ionic surfactants can be contained. The surfactant can also be biologically dissociative, for example by enzymatic dissociation of esterases. An example of such a surfactant, tetradekyl(oxycarbonyl)-N, N, N-trimethylmethaneaminium chloride (TeBo), is comprised in the examples of the invention and also has the advantage that the surfactant properties, which can have a certain harmful influence on the cornea in the eye, for instance on the epithelium is avoided by an enzymatic influence of esterases, localized in the cornea. The surfactant can also act as a preservative, in particular cationic substances are advantageous in this respect.

As drugs in the composition, drugs having a distribution coefficient $K_D > 10$ for octanol/water are preferred.

Furthermore, the composition can also contain suitable excipients, such as tonicity regulators, which can also be present to control the release of drugs from the gel formed, pH-regulators and preservatives.

The invention is illustrated in greater detail below with reference to the accompanying figures, wherein:

Fig. 1 shows graphically cumulatively released drug in % after a given time in hours for three different compositions of different content.

Fig. 2 shows graphically cumulatively released drug in % after a given time in hours for four different compositions of different content.

Fig. 3 shows graphically released drug after a given time in hours for the composition in example 8.

According to a preferred embodiment, polysaccharides are preferred as in situ-gel formers, in particular ethylhydroxy cellulose (EHEC), deacetylated gellan (Gelrite®), karrageenanes, alginates and hyaluronic acid.

According to an other preferred embodiment, one or more charged or uncharged surfactants are comprised, e. g.: TeBo (tetradekyl(oxycarbonyl)-N, N, N-trimethylmethaneammonium chloride), benzalconium chloride, SDS, sorbitane esters, polyetylene oxide sorbitane esters, cetrimide,

polyquade, glycerides, betaines, phospholipids, or the surfactant consists of a drug or a prodrug, which can be locally degradable at the administration site and additionally can have anti-bacteria properties and/or function as preservatives as well.

In yet another embodiment the pharmaceutical substance is chosen from drugs or prodrugs having surfactant properties and at the same time are used as surfactant.

Examples

A comparative test of compositions according to the invention to compositions, containing timolol, a comparatively soluble drug, was performed by graphically showing the release of drug after a given time. The compositions containing timolol show prior art and the object of the examples as follows is to show obvious improvements, i. e. long release duration of the compositions according to the invention.

All components comprised in the compositions were mixed in arbitrary order, except for the drug, which was added last, in given amounts, according to the examples.

The physiological electrolyte solution in the examples 1-3 is not necessary for any reason but practical i. e. in order to be able to perform the experiments without dropping into a real eye.

The tests were performed in that 4 grams of a gel was placed in a dissolution apparatus according to USP into a special cell therein. Receiving media was 0,9 % NaCl and the stirring rate was 20 rpm. The temperature was consistently 37 °C. On suitable occasions, as showed in Fig. 1-3, the concentration of drug was measured in the media. This concentration is plotted vs the time in hours in accompanying drawing figures 1-3, in which 100 % corresponds to total amount of drug originally existing in the gel.

The compositions 1 and 4 are comparative examples, with in water easily soluble drug.

Composition 1

2 mg timololmaleate
24 mg Gelrite® (Kelco Division of Merck, Sharp and Dohme)
0,8 mg benzalkonium chloride
physiological electrolyte solution (simulated tear liquid) ad 4g

Composition 2

2 mg hydrocortisone
24 mg Gelrite® (Kelco Division of Merck, Sharp and Dohme)
0,8 mg benzalkonium chloride
physiological electrolyte solution (simulated tear liquid) ad 4g

Composition 3

200 µg latanoprost
24 mg Gelrite® (Kelco Division of Merck, Sharp and Dohme)
0,8 mg benzalkonium chloride
physiological electrolyte solution (simulated tear liquid) ad 4 g

Composition 4

6	mg timololchloride
40	mg EHEC (DVT 89017, Akzo Nobel Surface Chemistry AB)
98	mg glycerol
11	mg SDS (sodium lauyl sulphate)

Composition 5

1,6	mg hydrocortisone
80	mg EHEC (DVT 89017, Akzo Nobel Surface Chemistry AB)
96	mg TeBo (tetradekyloxycarbonyl-N, N, N-trimethylmethaneaminium chloride), Akzo Nobel

water ad 4 g

Composition 6

4	mg dexametason
80	mg EHEC (DVT 89017, Akzo Nobel Surface Chemistry AB)
96	mg glycerol
40	mg TeBo (tetradekyloxycarbonyl-N, N, N-trimethylmethaneaminium chloride), Akzo Nobel

water ad 4g

Composition 7

200	µg latanoprost
40	mg EHEC (DVT 89017, Akzo Nobel Surface Chemistry AB)
13	mg CTAB (cetyltrimethylammonium bromide)

water ad 4 g

Composition 8

720	mg benzagine
77,6	mg EHEC (DVT 89017, Akzo Nobel Surface Chemistry AB)
100	mg glycerol
20	mg TeBo (tetradekyloxycarbonyl-N, N, N- trimetylmethaneaminium chloride), Akzo Nobel

water ad 4g

In Fig. 1 is graphically shown "in vitro" release for the compositions of examples 1-3. Composition 1, containing timolol, a in water relatively easily soluble substance, is released relatively fast, which is illustrated with circles in the figure. Composition 2, containing hydrocortisone is also released relatively fast, despite being regarded as lipophilic. Composition 3, on the contrary, containing latanoprost, which is very lipophilic, clearly shows a slow release rate, illustrating the invention.

Fig. 2 shows graphically "in vitro" release of EHEC "in situ"-gels of the compositions 4-7. Composition 4, containing timolol, is released relatively fast, while hydrocortisone is slightly slower. Latanoprost, which is a very lipophilic prostaglandineester and dexametason in the compositions 6 and 7 are released substantially slower illustrating the invention still further.

Fig. 3 shows graphically "in vitro" release for EHEC "in situ" gels of composition 8. Benzagine is a hard to dissolve (lipophilic) dye substance, which is released slower than timolol, showing the invention.

As demonstrated, the examples, show the object of the invention, i. e. to obtain a slow release of drug during a long time.

Even if only a small number of poorly soluble drugs have been illustrated in the examples, it is within the capacity of a person skilled in the art to choose other lipophilic drugs, and is therefore within the scope of the invention. The examples are not limiting, but are only intended to illustrate the invention.

Claims

1. An in situ gel forming pharmaceutical composition for local administration to a target organ in the body, said composition substantially consisting of an aqueous solution comprising one or more aggregate forming surfactants, one or more gel forming water-soluble polymers, a drug and optionally excipients, characterized in that the drug has lipophilic properties by means of binding stronger to the aggregates of surfactant than to water, whereby its release from the in situ formed gel to the target organ occurs slowly.

2. An pharmaceutical composition according to claim 1, characterized in that as said in situ gel forming polymer are used polysaccharides, in particular ethylhydroxy cellulose (EHEC), deacetylated gellan (Gelrite®), karrageenanes, alginates and hyaluronic acid.

3. An pharmaceutical composition according to claim 1 or 2, characterized in that said in situ gel forming polymer is present in an amount of 0,1-5 % by weight, based on the composition.

4. A pharmaceutical composition according to any one of the claims 1-3, characterized in that said surfactant is selected from tetradekyloxycarbonyl-N, N, N-trimetylmethaneaminium chloride, benzalkonium chloride, SDS, sorbitane esters, polyethylenoxide sorbitane esters, cetrimid, polyquad, glycerides, betaines and phospholipids.

5. A pharmaceutical composition according to any one of the claims 1-3, characterized in that the drug is selected from drugs or so called prodrugs having surfactant properties and simultaneously used as a surfactant.

6. A pharmaceutical composition according to claim 4, characterized in that said surfactant is present in an amount of 0,005-1,0 % by weight, based on the composition.

7. A pharmaceutical composition according to any one of the claims 1-6, characterized in that it comprises one or more lipophilic drugs and/or prodrugs, having a distribution coefficient larger than 10 in octanol/water.

8. A pharmaceutical composition according to any one of the claims 1-7, characterized in that it comprises conventional additives, such as pH-regulators, osmolality regulators, preservatives, anti-oxidants, complexants and viscosity regulators.

9. A pharmaceutical composition according to any one of the claims 1-8, intended for use for local administration to the mucous membranes of the body, in particular to the eye and/or nose, as well as for administration on the skin and/or parentally.

FIG 1

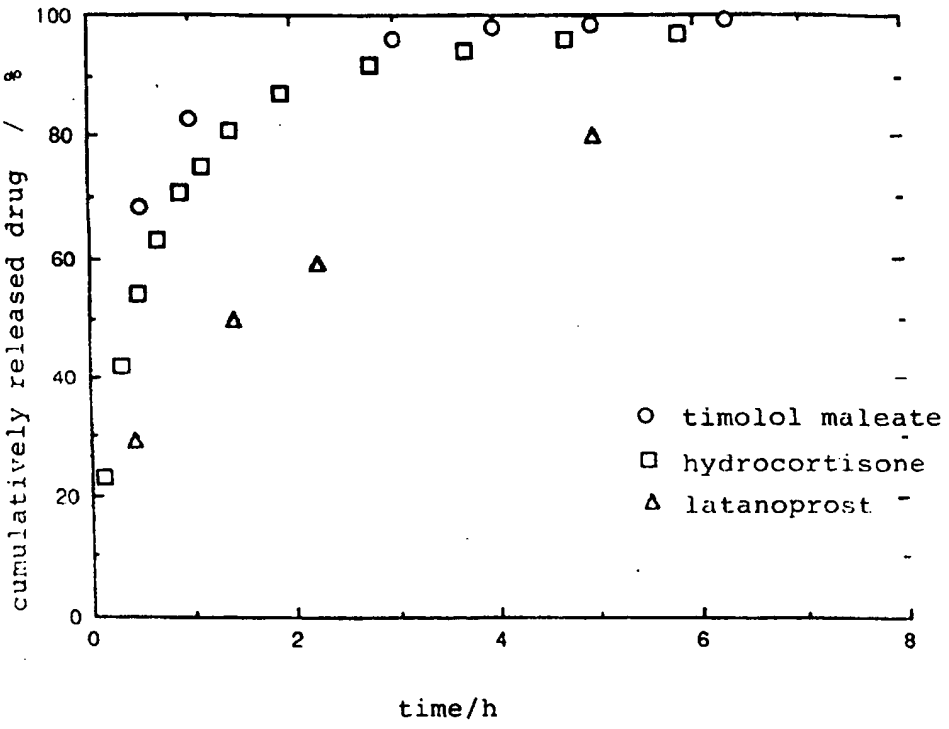

100
80
60
40
20
0
0
2
4
6
8
cumulatively released drug / %
time/h
timolol maleate
hydrocortisone
latanoprost

FIG 2

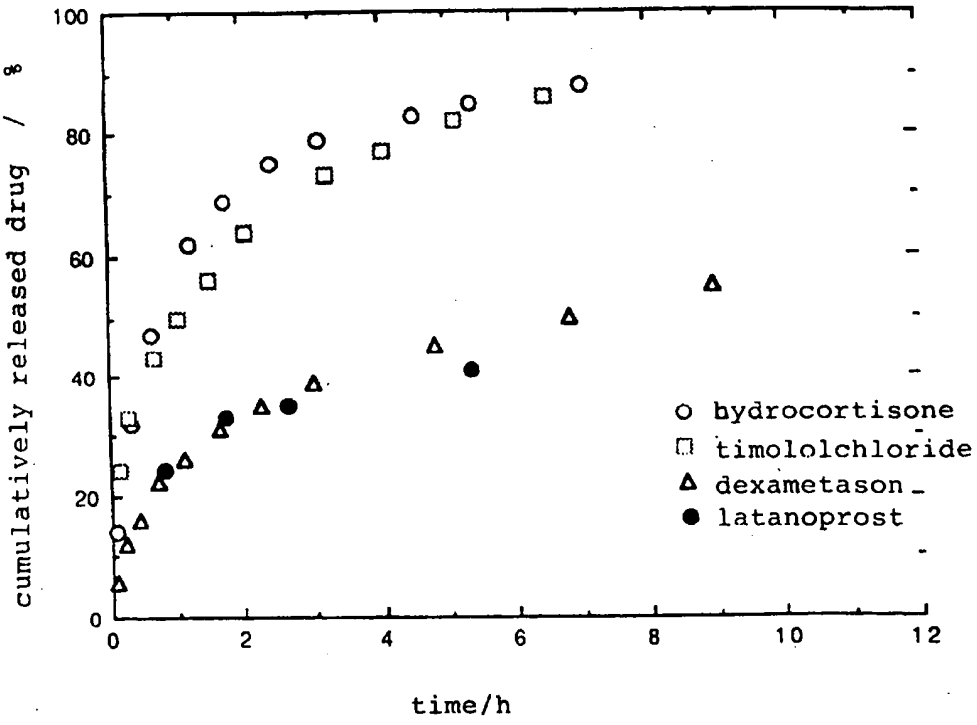
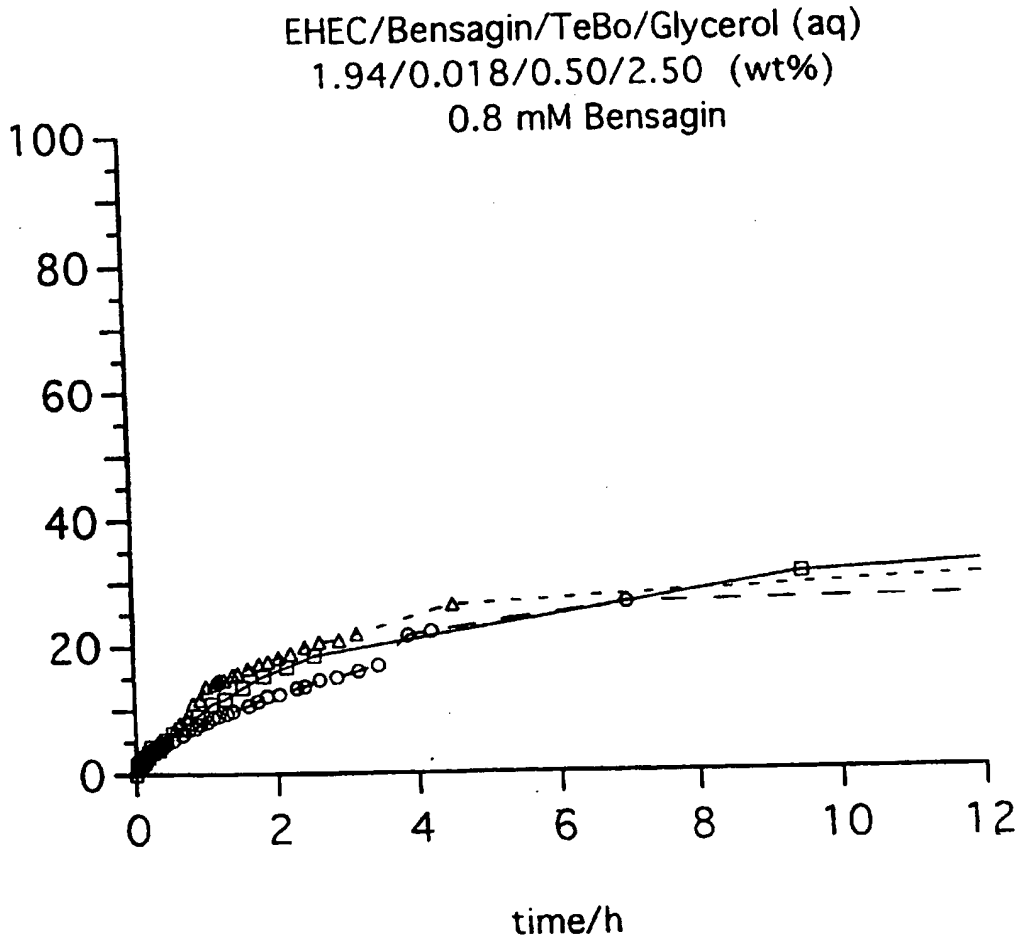

cumulatively released drug / %
100
80
60
40
20
0
0
2
4
6
8
10
12
time/h
hydrocortisone
timololchloride
dexametason
latanoprost

FIG 3


EHEC/Bensagin/TeBo/Glycerol (aq)
1.94/0.018/0.50/2.50 (wt%)
0.8 mM Bensagin
100
80
60
40
20
0
0
2
4
6
8
10
12
time/h

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01592

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/00, A61K 47/48, A61K 47/36, A61K 47/38
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE,CAPLUS,WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J.Soc.Cosmet.Chem., Volume 41, 1990, E.D.Goddard, "Polymer/surfactant interaction" page 23 - page 49 --	1-9
A	Macromolecules, Volume 29, 1996, B.Cabane et al, "Microphase Separation in Polymer + Surfactant Systems" page 3188 - page 3197 --	1-9
A	International Journal of Pharmaceutics, Volume 137, 1996, Katarina Edsman et al, "Rheological evaluation and ocular contact time of some carbomer gels for ophthalmic use" page 233 - page 241 --	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"B" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 1998	22 -01- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00